J Mol Model (2010) 16:799–804
DOI 10.1007/s00894-009-0627-6

ORIGINAL PAPER

Theoretical study on the molecular and electronic properties of some substances used for diabetes mellitus treatment

Vinicius G. Maltarollo · Paula Homem-de-Mello · Kathia M. Honório

Received: 6 July 2009 / Accepted: 15 November 2009 / Published online: 12 December 2009

Abstract Diabetes mellitus (DM) is a disease that affects a large number of people, and the number of problems associated with the disease has been increasing in the past few decades. These problems include cardiovascular disorders, blindness and the eventual need to amputate limbs. Therefore, the quality of life for people living with DM is less than it is for healthy people. In several cases, metabolic syndrome (MS), which can be considered a disturbance of the lipid metabolism, is associated with DM. In this work, two drugs used to treat DM, pioglitazone and rosiglitazone, were studied using theoretical methods, and their molecular properties were related to the biological activity of these drugs. From the results, it was possible to correlate the properties of each substance – particularly electronic properties – with the biological interactions that are linked to their pharmacological effects. These results suggest that there are future prospects for designing or developing new drugs based on the correlation between theoretical and experimental properties.

Keywords Diabetes mellitus · DFT · Drug design · Electronic properties · IEF-PCM

V. G. Maltarollo · P. Homem-de-Mello · K. M. Honório
Universidade Federal do ABC,
Rua Santa Adélia, 166,
Bairro Bangu 09210-170 Santo André - SP, Brazil

K. M. Honório (✉)
Escola de Artes, Ciências e Humanidades,
Universidade de São Paulo,
Av. Arlindo Bettio, 1000,
03828-000 São Paulo, SP, Brazil
e-mail: kmhonorio@usp.br

Introduction

Diabetes mellitus (DM) is a disease characterized as a chronic disorder affecting the metabolism of carbohydrates, lipids and proteins. Another feature of the disease is hyperglycemia due to the inappropriate use of glucose by the body. There are two variants of DM, type 1 and type 2. Specifically, type 2 diabetes occurs in adults and is defined by a disability of the pancreas related to the secretion of insulin and by peripheral insulin resistance [1–4]. The presence of DM symptoms results in high rates of morbidity and mortality, with significant losses in quality of life. DM is a cause of renal failure, lower limb amputation, blindness and cardiovascular disease [5, 6].

The family of nuclear receptors called peroxisome proliferator activated receptors (PPARs) is linked to the regulation of various metabolic processes, such as catabolism of lipids and metabolism of carbohydrates. Currently, three main subtypes of this nuclear receptor are known: PPARγ, PPARδ and PPARα. Therefore, substances that activate these receptors can be employed as drugs in DM treatment [7]. There are several drug treatments for diabetes, and among them are the glitazones, a drug class that activates the isoform PPARγ. The activation of these receptors stimulates the transcription of genes responsible for reducing insulin resistance, as well as genes responsible for hepatic glyconeogenesis. However, these drugs are not indicated for patients with any hepatic dysfunction because of their toxicity in the body [8].

Due to all of the aspects described above, there is a need for more effective treatments for DM. New drugs for the treatment of type 2 DM may arise from research and discoveries related to the PPARs as biological targets [9]. Therefore, the main objective of this study is to evaluate the behavior of two substances employed as drugs to treat DM

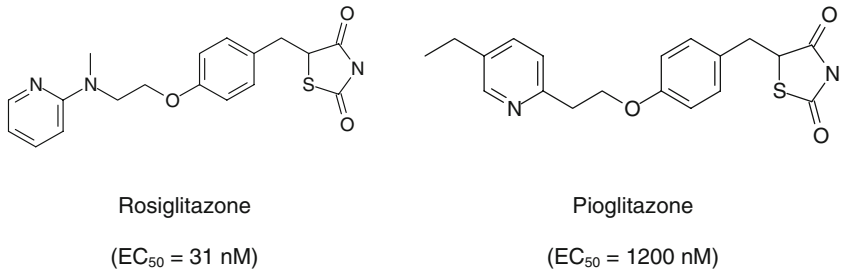

Fig. 1 Molecular structures of the studied compounds

using methods that characterize the molecular and electronic structure of these substances, providing information on possible mechanisms of interaction with the biological receptor under study.

Methodology

The substances studied in this work were rosiglitazone and pioglitazone, which are currently marketed for the treatment of DM [10, 11]. The molecular structures of these substances, along with their biological properties (EC_{50}, *i.e.*, the concentration of the compound that produces 50% of the possible maximum biological response) are shown in Fig. 1.

Geometry optimization and the calculation of electronic properties (total energy, energy of the frontier orbitals and dipole moment) were performed using density functional theory (DFT) [12–14]. We used the functional B3LYP [15–17] and DGDZVP basis sets as implemented in the computational package Gaussian03 [18]. The absence of imaginary frequencies was used as a criterion to ensure that the optimized structures represented the minimum in the potential energy surface.

The two substances studied here are employed as drugs to treat DM, because they activate PPARs. A strategy to handle such complex systems involves the use of dielectric continuum models to simulate the protein environment and/or the solvent [19–21]. It is very difficult to define properly the internal dielectric constant of the protein [20], so we have performed calculations in two organic solvents: ether and acetone. Table 1 shows the values of the dielectric constants for the solvents used in this work. We have compared these results to gas-phase and aqueous solution calculations. Solvation was simulated using the integral equation formalism of the polarizable continuum model (IEF-PCM) [22–24], which has been employed successfully to study many different systems, such as dyes [25, 26] and drugs [27–29].

Stereochemical properties (area and volume) and the partition coefficient (log P) for each geometry obtained were calculated using the module "QSAR", implemented in the HyperChem computational package.

Results and discussion

In order to analyze the effects of solvent on the structures, we have decided to compare all optimized geometries of each molecule and Fig. 2 displays the superposition of these structures. As can be seen in Fig. 2, there are no significant variations in the molecular conformations of the molecules based on different surroundings.

After the optimization study, the molecular and electronic properties were calculated and the values obtained are presented in Table 2.

From Table 2, it is evident that the total energy (E_T) diminishes as the dielectric constant increases; thus, polar solvents stabilize the studied glitazones. Frontier orbital energies (E_{HOMO} and E_{LUMO}) indicate the electron-donating and/or electron-accepting characteristics of the substances. Moreover, E_{HOMO} and E_{LUMO} values can indicate the formation of a charge transfer complex (CTC) between the compound and the biological receptor [31]. As presented in Table 2, these energies and the HOMO-LUMO gap are not significantly affected by solvation. Both glitazones present the same value for E_{LUMO}, but the E_{HOMO} values are quite different: the E_{HOMO} of rosiglitazone is greater than that of pioglitazone, indicating that rosiglitazone has more electron-donor character than does pioglitazone. As rosiglitazone is the most potent compound (EC_{50}=31 nM), the mechanism of interaction between rosiglitazone and the biological receptor is based on electron transfer from drug to protein, *i.e.*, rosiglitazone would be the electron-donor species due to its E_{HOMO} value.

For the glitazones studied in this work, it was found that a lower HOMO-LUMO gap corresponded to a more potent drug. This fact indicates that a smaller gap between the last occupied orbital and the first virtual orbital can promote an intramolecular electron transfer, allowing important inter-

Table 1 Dielectric constants of the solvents employed in this work

Solvent	Water	Acetone	Ether
Dielectric constant (ε)	78.39	20.7	4.335

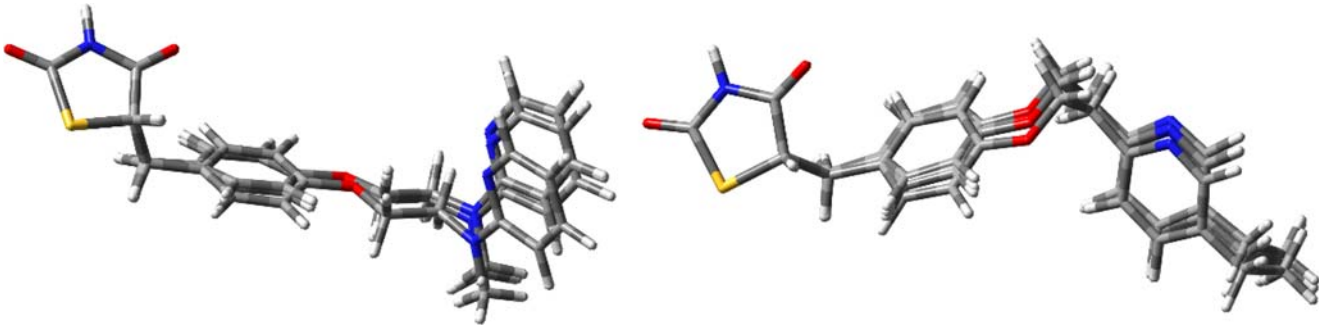

Fig. 2 Superposition of the optimized geometries of each molecule studied in the gas phase, water, acetone and ether

actions between the drug and its respective biological receptor.

From the dipole moment values (μ) presented in Table 2, we can see that rosiglitazone is more polar than pioglitazone. For both molecules studied, the dipole moment is significantly different in the gas phase than it is in solution. Figure 3 presents the dipole moment vectors for all structures obtained. As the polarity of the solvent diminishes, the dipole vector becomes more parallel to the structures. This can indicate that the electronic structure of the molecules studied can be rearranged depending on the polarity of the environment, facilitating the entrance of the drug into the active site. The large value of the dipole moment for rosiglitazone indicates that the polarity in different regions of the molecule favors hydrophilic interactions, increasing its affinity for specific residues in the active site. In fact, Pochetti et al. [32] demonstrated that the mechanism of interaction between the isoform PPARγ and a partial agonist, GW2331, is determined by important hydrogen bonds between the agonist and the following residues of the active site: histidine 323, histidine 449, serine 289 and tyrosine 473.

Analyzing the stereochemical properties displayed in Table 2, rosiglitazone has an average area equal to 535.34 A^2, and its average volume is 1019.76 A^3. For pioglitazone, the average area is equal to 532.43 A^2, and the average volume is 1035.98 A^3. The values of the properties cited above for the two molecules studied are very close, and it is possible to note that the values of volume (V) are inversely proportional to the biological activity, *i.e.*, the most potent

Table 2 Calculated properties for rosiglitazone and pioglitazone

Properties	Gas-phase	Ether (ε=4.335)	Acetone (ε=20.7)	Water (ε=78.39)
EC_{50}=31 nM[a] [30]	Rosiglitazone			
E_T (a.u.)	−1485.5854	−1485.6077	−1485.6181	−1485.6213
E_{HOMO} (a.u.)	−0.212	−0.210	−0.210	−0.210
E_{LUMO} (a.u.)	−0.048	−0.048	−0.048	−0.048
Gap[b] (a.u.)	0.164	0.162	0.162	0.162
μ (D)	5.285	5.957	6.284	6.491
A ($Å^2$)	536.58	535.56	534.41	534.82
V ($Å^3$)	1017.28	1019.84	1020.89	1021.03
log P	3.60	3.42	3.42	2.48
EC_{50}=1200 nM[a] [30]	Pioglitazone			
E_T (a.u.)	−1469.5517	−1469.5736	−1469.5838	−1469.5871
E_{HOMO} (a.u.)	−0.226	−0.224	−0.224	−0.225
E_{LUMO} (a.u.)	−0.048	−0.048	−0.048	−0.048
Gap[b] (a.u.)	0.178	0.176	0.177	0.178
μ (D)	3.702	4.144	4.330	4.399
A ($Å^2$)	533.41	532.31	531.58	532.42
V ($Å^3$)	1034.34	1035.91	1036.56	1037.11
log P	3.86	3.86	3.86	3.27

[a] EC_{50}=Concentration of the compound that produces 50% of the possible maximum biological response.

[b] Gap=E_{HOMO} - E_{LUMO}

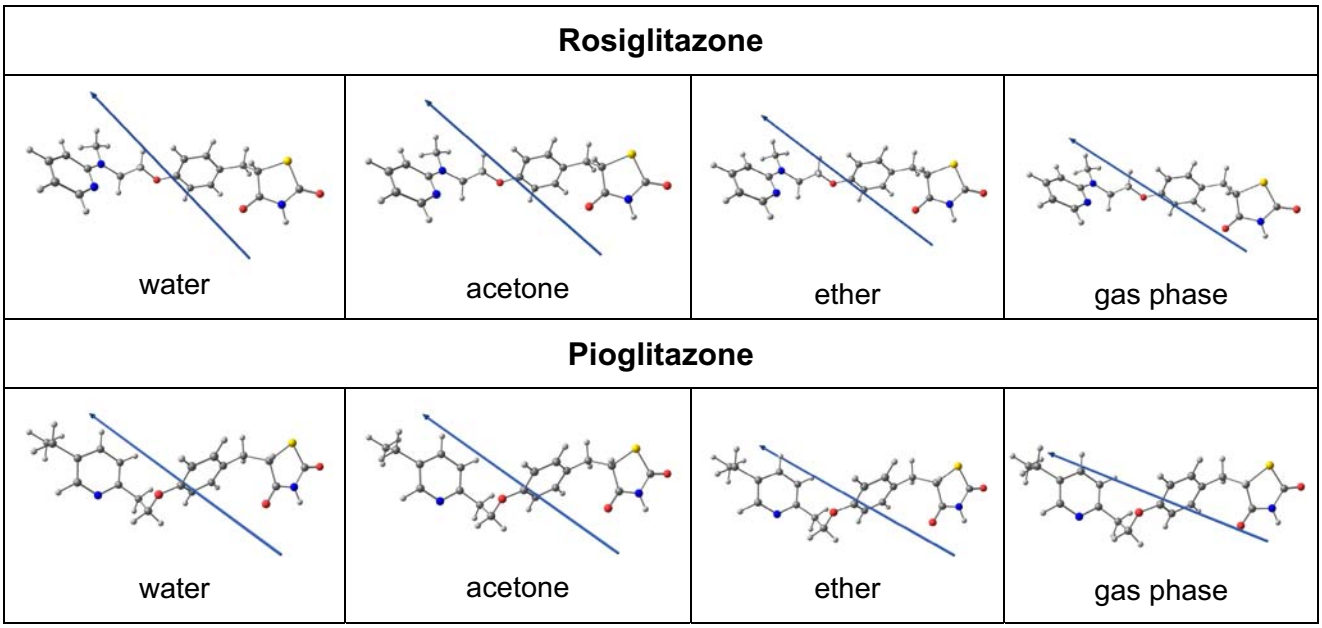

Fig. 3 Dipole moment vectors for each structure obtained

compound (rosiglitazone, EC_{50}=31 nM) has the smallest volume. This spatial property could indicate that more bulky molecules are not able to reach the active site of the protein.

Another important property for understanding the main interactions between a drug and its biological receptor is lipophilicity, which is normally evaluated by means of the logarithm of the partition coefficient (log P). As indicated in Table 2, log P values remain constant for structures obtained in gas-phase and organic solvents, but the structures obtained in aqueous solution have smaller values of log P. Comparing pioglitazone and rosiglitazone, the log P value of pioglitazone is slightly higher. Therefore, the greater hydrophobic character of pioglitazone reveals that some hydrophobic interactions in the active site can reduce the agonist behavior of the drug.

We also obtained a plot of the frontier molecular orbitals (HOMO and LUMO) in order to analyze the main atomic contributions for these orbitals. The importance of observing these plots was to determine which atoms were located at the possible sites of electronic transfer between the molecule under study and its biological target. Figure 4 shows the HOMO and LUMO plots of both substances studied considering only one solvent, as they are essentially identical for all the conformations obtained.

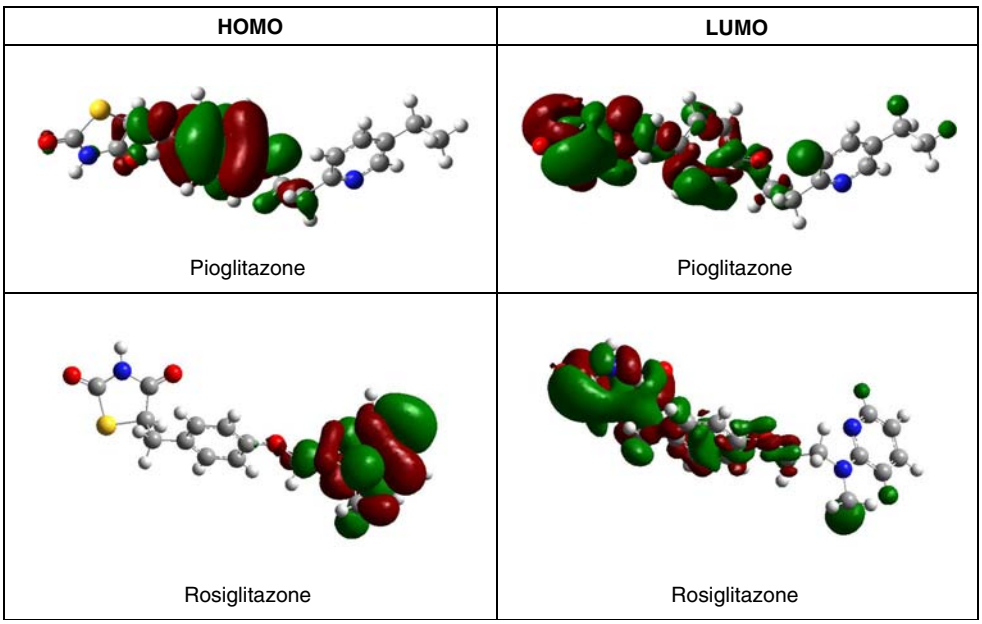

Fig. 4 HOMO and LUMO plots of each studied compound

From Table 2 and Fig. 4 it is possible to see that the LUMOs (energy and atomic contributions) of both molecules are very similar. However, as we have pointed out before, E_{HOMO} is very well correlated with the drug potency, as well as the atomic contributions for this orbital (*i.e.*, the HOMO contributions of pioglitazone are located at the central chain of the molecule, while the HOMO of rosiglitazone is located at the benzene ring). Therefore, due to the main differences in the atomic contributions for the HOMO and its respective energy, it is possible to say that electronic interactions (electron donor characteristics of molecules) between the substances analyzed and the aminoacid residues in the active site of the protein target are detrimental to the biological activity. In fact, as we have pointed out previously, the main interactions between a partial agonist and the isoform PPARγ are hydrophilic in character, *i.e.*, there are important hydrogen bonds between the agonist and the following residues in the active site: histidine 323, histidine 449, serine 289 and tyrosine 473 [32]. From the molecular structures of rosiglitazone and pioglitazone, it is possible to see that rosiglitazone has one more tertiary nitrogen atom, suggesting that an extra hydrogen bonding between the rosiglitazone and the polar amino residues in the ligand binding domain of PPARs [32] plays a critical role in the approximate 40 times higher EC_{50} value of rosiglitazone. From our outcomes, this fact can be related to higher E_{HOMO} and dipole moment values (energetic parameters) presented by the most potent compound (rosiglitazone), as it is also explored in other studies [33–35].

Conclusions

From this work, we can note that the variation of environment (solvent effects) does not influence the conformation and the molecular properties of the drugs studied. However, solvent effects seem to be important in evaluating the drug-protein electrostatic interactions, as evidenced by the variation of the dipole moment with the solvent used. Comparing the average values for the properties calculated by theoretical methods, it is possible to see that several molecular and electronic properties correlated well with the biological activity presented experimentally by two drugs marketed for the treatment of DM. From the values of E_{HOMO} and the main differences observed from the HOMO plots for both molecules, a mechanism of interaction between rosiglitazone (the most potent substance) and the biological receptor can be based on electron transfer from drug to protein – *i.e.*, rosiglitazone would be the electron-donor species due to its E_{HOMO} value. Another important observation is the polarity in different regions of the molecule, which favors hydrophilic interactions and increases the drug affinity for specific residues in the active site. Analyzing the stereochemical properties calculated, we can see that the most potent compound (rosiglitazone, EC_{50}= 31 nM) has the smallest volume, indicating that the most bulky molecules are not able to reach the active site of the protein. Therefore, these properties can help to understand the main features responsible for the interaction between a bioactive substance and its biological receptor and help in the design of new drugs for DM.

Acknowledgments We gratefully acknowledge the financial support from FAPESP (The State of São Paulo Research Foundation), CNPq (The National Council for Scientific and Technological Development) and CAPES (Coordination for the Improvement of High Education Personnel), Brazil.

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